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Analysis of susceptibility and drug resistance of antifungal agents in aspergillosis and mucormycosis patients: A Systematic review

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Corresponding author:
Wei Liu

liuwei@bjmu.edu.cn

Author Affiliation:
Department of Dermatology and Venerology, Peking University First Hospital, No.8 Xishiku Street,Xicheng District, Beijing, China.

Song, YG; Verweij, PE; Buil, JB; Hoog, SD; Liu, J; Guo, JX; Liu, W; Li, RY.

ADMINISTRATIVE INFORMATION

Support - MSD China.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - Jie Liu and Jiaxian Guo are employees of MSD China. All authors declared that there were no conflicts of interest.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 July 2024 and was last updated on 19 July 2024.

INTRODUCTION

Review question / Objective Primary objectives: Systematically collect susceptibility and drug resistance data for Aspergillosis (specifically Aspergillus fumigatus, Aspergillus flavus and Aspergillus niger) and mucormycosis (specifically Rhizopus spp., Mucor spp., and Rhizomucor spp.) against different types of antifungal agents (specifically Isavuconazole, Posaconazole, Amphotericin B, itraconazole, voriconazole).
Secondary objectives: Susceptibility and drug resistance data among different subgroups:
1. Between environmental and clinical isolates
2. In different patient populations.

Background Invasive fungal disease, especially aspergillosis and mucormycosis, is considered as one of the important causes of morbidity and mortality among a wide variety of patients with immunodeficiency, particularly in immunocompromised populations. Due to the increased use of antifungal agents, the epidemiology of invasive fungal infections has changed over the past years. According to a recent review of 851 cases over the period January 2000 through January 2017, in Asia, the incidence of mucormycosis is 31%. The recommended treatments for invasive fungal disease included antifungal agents such as posaconazole, itraconazole and amphotericin B, and surgery4. The mortality rate significantly differs depending on the immune condition of patients and different treatment regimens.

Rationale As aspergillus and mucor can be resistant to antifungal agents, the burden of antifungal resistance in high-risk patients is becoming one of the major concerns. Antifungal

drug-related factors, like in vitro susceptibility and drug resistance have an important bearing on the ultimate outcome of treatment and can help to predict clinical response to therapy. The susceptibility of antifungal agents varies from different regions. Currently, there is no systemic review or meta-analysis on antifungal agents' susceptibility despite plenty of data accumulated in literature. Evaluation of drug resistance characteristics is beneficial to selection of suitable drugs and dose of them for the clinician. A better understanding of the clinical impact of antifungal resistance is essential to the prompt and efficient treatment of patients with aspergillosis and mucormycosis and to improving the outcome of such infections.

METHODS

Strategy of data synthesis

PubMed
#1 "Aspergillus fumigatus"[Mesh] OR "aspergillus flavus"[Mesh] OR "aspergillus niger"[Mesh] OR "rhizopus"[Mesh] OR "rhizomucor"[Mesh] OR "mucor"[Mesh] OR "Aspergillus fumigatus"[tw] OR "aspergillus flavus"[tw] OR "aspergillus niger"[tw] OR "rhizopus"[tw] OR "rhizomucor"[tw] OR "mucor"[tw] OR "A. fumigatus"[tw] OR "a. flavus"[tw] OR "a. niger"[tw]
#2 "Antifungal Agents"[Mesh] OR "Drug Resistance, Fungal"[Mesh] OR Fungicid*[tw] OR Antifungal Agent*[tw] OR Antifungal Antibiotic*[tw] OR Anti-fungal Agent*[tw] OR Anti-fungal Antibiotic*[tw] OR antifungus agent*[tw] OR fungistatic agent*[tw] OR fungostatic agent*[tw] OR mycostatic agent*[tw] OR "isavuconazole" [Supplementary Concept] OR isavuconazole OR "BAL-8557" OR isavuconazonium OR Cresemba OR "posaconazole" [Supplementary Concept] OR posaconazole OR Noxafil OR "SCH-56592" OR "Amphotericin B"[Mesh] OR Amphotericin OR Fungizone OR Amphocil OR "Itraconazole"[Mesh] OR itraconazole OR canadiol OR candistat OR canditral OR hongoseril OR hyphanox OR itrac OR itralek OR itranax OR pulmazole OR "pur 1900" OR sporacid OR sporal OR sporonox OR triasporin OR R51211 OR Sporanox OR Orungal OR "Voriconazole"[Mesh] OR
voriconazole OR "UK 109496" OR Vfend OR "zp 059"
#3 "disease susceptibility"[Mesh] OR susceptibl*[tiab] OR susceptiv*[tiab] OR resist*[tiab] OR "hypersensitivity"[Mesh] OR hypersensitivit*[tiab] OR
sensitiv*[tiab] OR "sensitivity and specificity"[Mesh] OR specificit*[tiab] OR activity[tiab]
#4 #1 AND #2 AND #3
#5 #4 NOT ("Review" [Publication Type] OR "Review Literature as Topic"[Mesh] OR Review[ti])
#6 #5 and ("2010/01/01"[Date - Publication] : "3000"[Date - Publication])
Embase
#1 'Aspergillus fumigatus'/exp OR 'Aspergillus flavus'/exp OR 'Aspergillus niger'/exp OR 'Rhizopus'/exp OR 'Rhizomucor'/exp OR 'Mucor'/exp OR ("Aspergillus fumigatus" OR "aspergillus flavus" OR "aspergillus niger" OR "rhizopus" OR "rhizomucor" OR "mucor" OR "A. fumigatus" OR "a. flavus" OR "a. niger"):ab,ti,kw
#2 'antifungal resistance'/exp OR 'isavuconazole'/exp OR 'posaconazole'/exp OR 'amphotericin B'/exp OR 'itraconazole'/exp OR 'voriconazole'/exp OR (Fungicid* OR ((Antifungal OR "Anti-fungal" OR antifungus OR fungistatic OR fungostatic OR mycostatic) NEAR/2 (Agent* OR drug OR drugs OR Antibiotic*)) OR isavuconazole OR "BAL-8557" OR isavuconazonium OR Cresemba OR posaconazole OR Noxafil OR "SCH-56592" OR Amphotericin OR Fungizone OR Amphocil OR itraconazole OR canadiol OR candistat OR canditral OR hongoseril OR hyphanox OR itrac OR itralek OR itranax OR pulmazole OR "pur 1900" OR sporacid OR sporal OR sporonox OR triasporin OR R51211 OR Sporanox OR Orungal OR voriconazole OR "UK 109496" OR
Vfend OR "zp 059"):ab,ti,kw
#3 'sensitivity and specificity'/exp OR (susceptibl* OR susceptiv* OR resist* OR hypersensitivit* OR sensitiv* OR specificit* OR activity):ab,ti
#4 #1 and #2 and #3
#5 #4 not ([review]/lim OR 'review'/exp OR review:ti)
#6 #5 AND [2010-2022]/py
Cochrane library
#1 MeSH descriptor: [Aspergillus fumigatus] explode all trees
#2 MeSH descriptor: [Aspergillus flavus] explode all trees
#3 MeSH descriptor: [Aspergillus niger] explode all trees
#4 MeSH descriptor: [Rhizopus] explode all trees
#5 MeSH descriptor: [Rhizomucor] explode all trees
#6 MeSH descriptor: [Mucor] explode all trees
#7 "Aspergillus fumigatus" OR "aspergillus flavus" OR "aspergillus niger" OR "rhizopus" OR "rhizomucor" OR "mucor" OR "A. fumigatus" OR "a. flavus" OR "a. niger"
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH descriptor: [Antifungal Agents] explode all trees
#10 MeSH descriptor: [Drug Resistance, Fungal] explode all trees
#11 MeSH descriptor: [Amphotericin B] explode all trees
#12 MeSH descriptor: [Itraconazole] explode all trees

#13 MeSH descriptor: [Voriconazole] explode all trees
#14 (Fungicid* OR ((Antifungal OR "Anti-fungal" OR antifungus OR fungistatic OR fungostatic OR mycostatic) NEAR/2 (Agent* OR drug OR drugs OR Antibiotic*)) OR isavuconazole OR "BAL-8557" OR isavuconazonium OR Cresemba OR posaconazole OR Noxafil OR "SCH-56592" OR Amphotericin OR Fungizone OR Amphocil OR itraconazole OR canadiol OR candistat OR canditral OR hongoseril OR hyphanox OR itrac OR itralek OR itranax OR pulmazole OR "pur 1900" OR sporacid OR sporal OR sporonox OR triasporin OR R51211 OR Sporanox OR Orungal OR voriconazole OR "UK 109496" OR Vfend OR "zp 059"):ti,ab,kw
#15 #9 or #10 or #11 or #12 or #13 or #14
#16 MeSH descriptor: [Disease Susceptibility] explode all trees
#17 MeSH descriptor: [Disease Susceptibility] explode all trees
#18 MeSH descriptor: [Sensitivity and Specificity] explode all trees
#19 (susceptibl* OR susceptiv* OR resist* OR hypersensitivit* OR sensitiv* OR specificit* OR activity):ti
#20 (susceptibl* OR susceptiv* OR resist* OR hypersensitivit* OR sensitiv* OR specificit* OR activity):ab
#21 #16 or #17 or #18 or #19 or #20
#22 #8 and #15 and #21.

Eligibility criteria

Population:

Studies about infections by Aspergillus fumigatus; Aspergillus flavus; Aspergillus niger; Rhizopus spp.; Mucor spp. or Rhizomucor spp.

Intervention:

Studies about antifungal agents with Posaconazole, Isavuconazole, Itraconazole Voriconazole, Amphotericin B

Outcomes:

Susceptibility, drug resistance, MIC (minimum inhibitory concentration); Studies that do not report any susceptibility and resistance outcomes were excluded. For example: phenotypic and genotypic analysis; synthesis of antifungal agents; resistance mechanism; genomic diversity; bacterial structure; Studies reporting only resistance results and sensitivity results other than MIC data were excluded; Studies about the testing method for susceptibility were excluded. (Testing methods: broth dilution, disk diffusion etc.)

Study design: in vitro study was included. Reviews, systematic reviews, and animal studies were excluded.

Time: Studies published before 2010 were excluded.

Other: Molecular test must be performed before the analysis, so that the classification of fungus has standard criteria. Articles that did not use molecular test were excluded.

Source of evidence screening and selection Two qualified reviewers, preferably experts in the field of infectious diseases, independently screened the abstracts and full-texts for eligibility of inclusion. The remaining articles were screened by two independent reviewers in order to ensure that they met prespecified study inclusion criteria, disagreement were resolved by the third reviewer. A PRISMA flow diagram were presented after study screening.

Data management All data collected for the study should be recorded accurately, promptly, and legibly. Endnote was used to store and manage references and to create bibliographies; Microsoft excel and word was used as tools for data collection and analysis. All data was recorded properly according to the nature of the data. The investigator or qualified designee was responsible for recording and verifying the accuracy of study data.

This is a narrative evidence synthesis, no inferential statistics, but summary statistics was conducted. We summarized the MIC data for each type of fungus of interest according to each type of anti-fungal agents. When clinical breakpoint value was proposed based on CLSI or EUCAST guidelines, MIC was interpreted based on CLSI/EUCAST standards. The MIC data in our study was compared with the cut-off value proposed by CLSI or EUCAST guidelines and the therapy outcome was predicted based on these results. In the absence of clinical breakpoints, according to Astvad 20227, after ascertain that the species identification is correct, we compared the MICs to existing MIC distributions for that drug and species to determine if MIC is most likely “normal” or “elevated”. Then we proposed a pragmatic categorization and upper limits for these species based on the comparison to modal MIC and range obtained for common species.

Language restriction No restriction.

Country(ies) involved China.

Keywords antifungal agents; susceptibility, resistance, Aspergillus, Mucorales.

Contributions of each author

Author 1 - Yinggai Song drafted the paper.
Email: syg3515@163.com

Author 2 - Paul E Verweij performed data collection, extraction and reviewed the manuscript.
Email: paul.verweij@radboudumc.nl
Author 3 - Jochem B Buil performed data collection, extraction and reviewed the manuscript.
Email: jochem.buil@radboudumc.nl
Author 4 - Sybren de Hoog contributed to the development of the selection criteria.
Email: sybren.dehoog@radboudumc.nl
Author 5 - Jie Liu obtained the funding and provided the administrative, technical and logistic support.
Email: jie.liu3@merck.com
Author 6 - Jiaxain Guo obtained the funding and provided the administrative, technical and logistic support.
Email: jia.xian.guo@merck.com
Author 7 - Wei Liu conceived the ideas and designed of the study.
Email: liuwei@bjmu.edu.cn
Author 8 - Ruoyu Li conceived the ideas and designed of the study.
Email: mycolab@126.com